

Reviewer 1: The revision "Genetic variation of hepatitis B virus and its significance for pathogenesis" Zhen-Hua Zhang et al " is well documented and can be very interesting to researchers in HBV infection. However it has two important limitations that should be resolved in order to be useful for publication.

1. In the section on HBV genotypes and subtypes no mention of the intergenotype recombination is observed, being this phenomenon very relevant Shi Virol 2012;427:51-9, Pourkarim WJG 2014; 20(23):7152-68.). As for instance the case of Ba genotype which is a recombinatgion of h genotype B with core region of genotype C (Sagauchi J Virol 2002; 76 (12): 5985-92)

A: Thanks for the suggestions. We have added the statements about the intergenotype recombination, "Notably, the intergenotype recombination has also been described previously, which plays an important role in the evolutionary history of HBV. Recombination is favoured in particular geographical regions [29, 30]. For instance, B/C recombinants are prevalent in Southeast Asia and East Asia [31]. Other intergenotype recombinants such as A/D, A/E, C/D and G/C recombinants have also been observed in different geographical regions so far". Related references have been cited according to the reviewer's comments (Page 6-7).

2. The section devoted to variants of the X region is very poor in comparisson with other sections such as Surface variants section (peerhaps by the own experience of authors) . This X region section should be significantly completed mainly with data avbout variants with insertions and deletions, which are well known from the late 90s as well as its presence in viral genomes inserted in patients with lesions severe and even hepatocarcinoma.

A: Thanks for the suggestions. We have added the statements about variants with insertions in X region, "In addition to truncated HBxAg mutants, insertions in the HBx gene may play a pivotal role in hepatocarcinogenesis. A Korean cohort study showed that the prevalence of insertions was significantly higher in patients with severe liver disease, HCC, or cirrhosis of the liver compared to patients who were carriers or had chronic hepatitis. Four novel types of insertions including PKLL, GM, FFN, and tt, were observed in six patients, which were accompanied by double mutations in the BCP region". Related references have been cited. (Page 23-24).

Reviewer 2: This paper reviews "Genetic variation of hepatitis B virus and its significance for pathogenesis".The manuscript is well presented and of interest and can contribute to increase the knowledge of this topic.

A: Thanks a lot!